SMALL-AIRWAYS DYSFUNCTION IN NONSMOKERS CHRONICALLY EXPOSED TO TOBACCO SMOKE

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Abstract We evaluated the effect of long-term passive smoking (involuntary inhalation of tobacco smoke by nonsmokers) and long-term voluntary smoking on specific indexes of pulmonary function in 2100 middle-aged subjects. Regardless of sex, nonsmokers chronically exposed to tobacco smoke had a lower forced mid-expiratory flow rate (FEF 25 to 75 per cent) and forced end-expiratory flow rate (FEF 75 to 85 per cent) than nonsmokers not exposed ($P<0.005$). In addition, values in passive smokers were not significantly different from those in light smokers and smokers who did not inhale ($P<0.005$). When we looked at the extent to which smoke exposure is related to graded abnormality, we found that nonsmokers in smoke-free working environments have the highest scores on the spirometric tests; passive smokers, smokers who do not inhale, and light smokers score similarly and significantly lower; and heavy smokers score the lowest ($P<0.005$). We conclude that chronic exposure to tobacco smoke in the work environment is deleterious to the nonsmoker and significantly reduces small-airways function. (N Engl J Med. 1980; 302: 720-3.)

IT is generally believed that infrequent and short-term exposure to pollutants in tobacco, such as carbon monoxide, nicotine, benzo(a)pyrene, and oxides of nitrogen, will not permanently alter pulmonary function in healthy adult nonsmokers. We tested two hypotheses: that nonsmokers chronically exposed at work to the pollutants in tobacco will score lower on tests of small-airways function than nonsmokers not chronically exposed to tobacco smoke; and that exposure to tobacco smoke will cause a graded abnormality in small-airways function in relation to the extent of smoke exposure.

METHODS

Subjects

To examine these hypotheses we used the scores on tests of mean forced mid-expiratory flow (FEF 25 to 75 per cent) and mean forced end-expiratory flow (FEF 75 to 85 per cent); these tests have proved effective in detecting small-airways disease in its early stages.[1-3] Forced vital capacity and forced expiratory volume in one second (FEV_1) were also studied.

Data were collected on 5210 cigarette smokers and nonsmokers who had been physiologically evaluated during a "Physical Fitness Profile" course sponsored by the Department of Physical Education, University of California, San Diego, between 1969 and 1979. Most of the subjects resided in San Diego, an area low in air pollution. Occupation and locations of work and residence according to zip codes were analyzed. There were no statistically significant differences between the groups in types of occupation or in working or living locations. Eighty-three per cent of the working subjects held professional, managerial, or technical positions, and the remainder were blue-collar workers. Personal habits, environmental pollution, and smoking habits were assessed from an extensive, self-administered questionnaire completed on two separate occasions. The reliability coefficients for the test and retest are greater than $r = 0.96$. Each subject's age, height, and weight were recorded, and they were categorized according to sex, exposure to tobacco smoke, and smoking habits.

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From the original 5210 candidates, 2208 were disqualified because they indicated on the questionnaire that they had a history of pulmonary or cardiac disease, persistent cough, recent asthma, respiratory illness, or bronchial disturbances; that they had had occupational exposure to dust or other toxic fumes; that they had lived in a smoggy or industrial area; or that they had been employed in areas associated with industrial pollution. The 3002 remaining candidates were assigned to one of six groups according to their exposure to tobacco smoke (Table 1). From each group 200 men and 200 women were then randomly selected and assigned to the comparison groups. However, only 50 male and female subjects were available for the noninhaling smoking group (3), and so the total number of subjects reported on is 2100.

A single technician administered successive forced-vital-capacity maneuvers until reproducible curves were obtained on each subject with use of the Donti Pulmonary Performance Analyzer (PA70). The fast vital-capacity spirogram achieving the greatest volume was used to calculate the forced vital capacity (FVC), the forced expiratory flow for one second (FEV_1), the forced mid-expiratory flow (FEF 25 to 75 per cent), and the forced end-expiratory flow (FEF 75 to 85 per cent) (Table 1).

Comparisons were made between the scores achieved by six groups of subjects matched for age and sex. Group 1 comprised nonsmokers who had neither lived in a house where tobacco smoking was permitted nor been employed in an enclosed working area that permitted smoking or routinely contained tobacco smoke. Group 2 comprised passive smokers, that is, nonsmokers who lived in a house where tobacco smoking was not permitted but had been employed for 20 years or more in an enclosed working area that permitted smoking and routinely contained tobacco smoke. Group 3 contained pipe, cigar, or cigarette smokers who did not inhale; Group 4, light smokers who had inhaled one to 10 cigarettes per day for 20 years or more, Group 5, moderate smokers who had inhaled 11 to 39 cigarettes per day for 20 years or more; and Group 6, heavy smokers who had inhaled more than 40 cigarettes per day for 20 years or more. Presumably, the subjects in these last four groups all worked in environments where smoking was permitted, since they themselves smoked at work.

To test the hypothesis that there was no difference between the pulmonary scores in each group, we used a statistical package called "SPSSH Release 6.02," which gave us a one-way analysis of variance. When the analysis of variance revealed a significant difference, the hypothesis was rejected. We then used the Student-Newman-Keuls multiple-comparison test to determine subgroups.[4]

Carbon Monoxide Levels in Working Environment

On the questionnaire the subjects who did not smoke indicated whether smoking was permitted in their working area and whether the air generally contained tobacco smoke. To obtain a more objective measure of true concentrations of smoke in the working areas, we placed a portable carbon monoxide analyzer (Ecolyzer, Ener-

Table 1. Vital Capacities and Expiratory Flow Rate (Mean ±S.D.) in Male and Female Smokers and Nonsmokers.

Group	No. of Subjects	Sex	Age	Height	FVC		FEV_1		FEF 25–75%		FEF 75–85%	
			yr	cm	liters	% predicted	liters	% predicted	liter/sec	% predicted	liter/sec	% predicted
1 — Nonsmokers, no smoky environment	200	F	47.77±7.0	162.05±6.58	3.35±0.63	102	2.63±0.63	104	3.17±0.74	108	1.03±0.38	112
	200	M	48.8±7.59	176.3±7.77	4.91±0.75	102	3.72±0.65	103	3.78±0.79	104	1.22±0.35	120
2 — Nonsmokers, smoky environment > 20 yr	200	F	45.91±6.94	161.8±6.68	3.23±0.46	98	2.47±0.63	99	2.72±0.71*	93	0.78±0.36*	85
	200	M	49.1±7.61	176.02±6.55	4.78±0.77	99	3.54±0.61	98	3.30±0.77*	91	0.97±0.34*	95
3—Smokers not inhaling cigarettes, pipe, or cigars > 20 yr	50	F	46.93±7.10	159±7.09	3.19±0.52	97	2.49±0.74	99	2.71±0.87*	92	0.78±0.43*	85
	50	M	47.6±7.38	174.5±7.42	4.63±0.86	96	3.56±0.76	99	3.32±0.86*	92	0.89±0.47	87
4 — Smokers inhaling 1–10 cigarettes per day > 20 yr	200	F	47.36±7.0	159.77±7.44	3.15±0.39	96	2.40±0.62	98	2.63±0.73*	89	0.76±0.31*	83
	200	M	48.5±7.51	175.9±7.44	4.58±0.77*	95	3.49±0.62*	97	3.23±0.78*	89	0.79±0.36*	77
5 — Smokers inhaling 11–39 cigarettes per day > 20 yr	200	F	45.72±6.87	160±6.99	2.80±0.38*	85	2.13±0.62*	85	2.29±0.70*	78	0.63±0.31*	69
	200	M	48.3±7.49	176.02±7.67	4.04±0.74*	84	3.08±0.61*	86	2.73±0.81*	76	0.69±0.29	68
6 — Smokers inhaling >40 cigarettes per day > 20 yr	200	F	45.98±6.73	159.26±7.29	2.55±0.38*	78	2.01±0.64*	80	2.12±0.72*	72	0.57±0.33*	62
	200	M	47.8±7.44	176.53±7.9	3.92±0.73*	82	2.77±0.60*	77	2.59±0.82*	72	0.61±0.31*	60
Prediction for age: 46.8 yr, height 160.53 cm †	1050	F	46.61±6.94	160.3±6.99	3.28	—	2.52	—	2.94	—	0.92	—
Prediction for age: 48.3 yr, height 175.77 cm †	1050	M	48.35±7.50	175.77±7.54	4.81	—	3.60	—	3.62	—	1.02	—

*Significantly different from values in nonsmokers ($P > 0.005$). †Predicted according to Morris.[11]

getics Science, Elmsdorf, N.Y.) on top of the desk or in the working area of 40 randomly selected nonsmokers who had indicated that they worked in an environment without smoke and 40 similarly selected nonsmokers who had indicated that the air in their working area contained smoke from co-workers. Carbon monoxide, a component of tobacco smoke, is an accurate tobacco-smoke tracer,[5-7] and its concentration is directly proportional to that of tobacco smoke.[8,9] The mean carbon monoxide concentrations in areas where smoking occurred were compared with similar measurements taken in areas where smoking was not permitted (Table 2). During the day, particularly at 11:20 a.m. and 1:20 p.m., the differences in the mean values between environments with and without smoking were significantly different. Only at 7:00 a.m. and 7:00 p.m., before and after working hours, were carbon monoxide concentrations the same. In the environments where there was smoking, the mean concentration at peak values almost doubled, from 6.4 to 11.6 parts per million, whereas in the environments where there was no smoking, the increase was from 6.3 to 8.2 parts per million. The peak concentration of carbon monoxide was significantly greater in the environments where smoking occurred. The carbon monoxide analyzer was calibrated in the laboratory and found to have ±2 per cent reproducibility and ±2 per cent accuracy at levels between 0 and 50 parts per million.

Of the 80 working areas tested for carbon monoxide concentrations, 76 were air-conditioned. No attempt was made to determine the direction of the circulation of refrigerated air or the exact air exchange. Building codes require a minimum of five to six complete air exchanges per hour. The size of the rooms and the number of coworkers in the working areas were computed. In terms of these two factors, there was no significant difference between the working areas where smoking was permitted and where it was not permitted. In the areas without smoking, ventilation was sufficient to maintain peak carbon monoxide concentrations below 9 parts per million, which Holbrook defines as the upper limit for carbon monoxide in areas with adequate ventilation.[10] However, ventilation in our study was not capable of adequately extracting polluted air as measured by carbon monoxide levels in areas where smoking was allowed (Table 2).

Results

The mean values ± the standard deviation for the FVC, FEV_1, FEF 25 to 75 per cent, and FEF 75 to 85 per cent in the six groups studied are shown in Table 1. There were no statistical differences in the ages and heights within the various groups.

Compared with nonsmokers who worked in environments where there was no smoking, both the men and the women in the other five groups had significantly lower values for FEF 25 to 75 per cent and FEF 75 to 85 per cent. These lower levels were observed in both absolute values and per cent predicted values calculated according to the formulas of Morris.[11] The FVC and FEV_1 were not as sensitive, and values were lower only in the female heavier smokers of Groups 5 and 6 and in the male heavier smokers of Groups 4, 5,

Table 2. Carbon Monoxide Concentrations (parts per million) Measured during the Workday.

Time	Smoking Permitted in Work Area (40 Subjects)		Smoking Not Permitted in Work Area (40 Subjects)		Comparison between Working Areas
	mean ±S.D.	Range	mean ±S.D.	Range	T value
7:00 a.m.	6.4±2.9	3.1–10.9	6.3±1.7	3.3–10.3	0.1
10:00 a.m.	9.2±5.4	3.5–29.4	7.1±3.3	3.6–13.6	2.1*
11:50 a.m.	11.1±6.0	4.1–21.2	8.2±4.1	3.8–12.7	2.9†
1:20 p.m.	11.6±7.3	3.8–25.8	6.9±2.7	4.0–13.8	4.7†
4:20 p.m.	9.7±5.9	3.3–20.2	7.5±3.8	3.3–11.9	2.2*
7:00 p.m.	7.1±3.3	3.2–14.7	6.5±2.2	3.4–10.7	0.6

*$P = 0.05$ by unpaired t-test. †$P = 0.01$ by unpaired t-test.

and 6. The passive smokers not only scored significantly lower than their nonsmoking counterparts but also fell into the same state of impaired performance as the noninhalers and light smokers. Again, this was true for both men and women.

Table 1 shows the predicted values for the average man and woman according to height and weight. There is no statistical difference between these predicted values and the values in nonsmokers. However, as the degree of smoking exposure increased in both men and women, the performance of FEF 25 to 75 per cent and FEF 75 to 85 per cent decreased, as shown by the stepwise reduction in scores for moderate and heavy smokers (Table 1).

As shown in Table 3, differences in pulmonary performance between groups were analyzed by statistical analyses of variance according to the Student-Newman-Keuls multiple-range test at a level of 0.005.[4] The subgrouping indicates that both male and female nonsmokers who live and work in a smoke-free environment score the highest of all the subgroups, and that passive smokers, smokers who do not inhale, and light smokers are not significantly different from one another. The analysis also shows that both moderate and heavy smokers are, in general, not significantly different: that is, they share about the same degree of dysfunction. It is impressive that in all pulmonary-function tests, the moderate and heavy smokers scored significantly worse than all other groups, and that in tests that best reflect small-airways function (FEF 25 to 75 per cent and FEF 75 to 85 per cent), the nonsmokers scored significantly better than all other groups.

Table 3. Pulmonary Function in Subjects Chronically Exposed to Tobacco Smoke.*

Variable	Sex	Subgroups Arranged in Order of Decreasing Pulmonary Function
FVC	Female	NS NI LS PS MS HS
	Male	NS PS NI LS MS HS
FEV_1	Female	NS NI LS PS MS HS
	Male	NS NI PS LS MS HS
FEF 25–75%	Female	NS PS NI LS MS HS
	Male	NS NI PS LS MS HS
FEF 75–85%	Female	NS PS NI LS MS HS
	Male	NS NI PS LS MS HS

*Underlinings indicate subgroups arranged by the Student-Newman-Keuls multiple-range test at the 0.005 level. For example, for FVC, female, there are three groups that differ from each other statistically; the first group comprises NS, NI, LS, and PS, the second group MS, and the third HS. NS denotes nonsmokers, PS passive smokers, NI noninhaling smokers, LS light smokers (one to 10 cigarettes per day), MS moderate smokers (11 to 39 cigarettes per day), and HS heavy smokers (40 or more cigarettes per day) — Groups 1 to 6, respectively.

Discussion

We used several methods to minimize the standard error of the difference and eliminate sampling biases in this study. First of all, measurements were made in a large number of subjects (a total of 2100), and they were divided into six specific groups according to their responses to a questionnaire on smoking history. Candidates with health, environmental, or occupational conditions that could influence pulmonary function adversely were disqualified from the study. Furthermore, comparisons among the groups of occupations and working and living locations showed that they were not significantly different, thus minimizing the sampling error. When the sites for measurement of carbon monoxide were selected, bias was reduced because 20 male and 20 female nonsmokers and 20 male and 20 female passive smokers were randomly selected from the 200 subjects in each group. Finally, most studies on smoking have a correlational design; this approach may weaken many of the conclusions because tobacco smoking is a matter of choice and is done for a variety of personal reasons, which may cause both the smoking and the pulmonary dysfunction. In our study, neither the nonsmokers nor the passive smokers chose to smoke; therefore, the pulmonary dysfunction found in passive smokers cannot be attributed to the "reasons" that may be related to the dysfunction in smokers. Comparison between the nonsmokers and the passive smokers is thus truly experimental.

Although there was no statistical difference between the predicted values in Table 1 and values in the nonsmokers, it must be remembered that predicted values were based on the combination of data obtained from nonsmokers and passive smokers. When data on the nonsmoker and the passive smoker are arithmetically averaged, the value approximates that found in existing predicted norms. We believe that in choosing subjects for establishing "normal predicted values," one should take into account the degree of cigarette pollution in which the subjects live and work.

Ambient carbon monoxide may have deleterious effects on bodily functions other than those of the lung. Studies by Bridge and Corn[9] and by Hexter and Goldsmith[12] have indicated that concentrations of carbon monoxide as low as 8 parts per million can increase the incidence of symptomatic or overt ischemic heart disease. It has also been shown that elevated carbon monoxide concentrations can increase the incidence of early angina in patients with atherosclerotic heart disease.[13,14] High carbon monoxide concentrations also lead to alterations in psychomotor performance in healthy subjects.[15] We chose to look at long-range changes in the function of small airways in the lungs of nonsmokers chronically exposed to low levels of tobacco smoke as measured by carbon monoxide levels. Carbon monoxide was used as an index of exposure to

tobacco smoke and was not intended to be identified as the specific inciting agent.

The traditional spirometric tests of FVC and FEV_1 depend mostly on the total airway resistance and elastic recoil of the lung and are often normal in the presence of extensive small-airways disease.[16] In contrast, the mid-expiratory and maximal end-expiratory flow rates reflect expiratory flow in the presence of lower lung volumes during a period when airway segments may be in the process of closing.[17,18] Other studies have indicated a high frequency of small-airways disease in relatively asymptomatic cigarette smokers.[19] In one study, 72 per cent of the subjects had significantly decreased maximal mid-expiratory flow rates.[1] Morris[2,20] has shown that measurements of forced expiratory flow rate are simple and accurate predictors of changes in small airways. It is generally agreed that in the presence of normal FVC and FEV_1, reduced forced mid-expiratory and end-expiratory flow rates are commensurate with small-airways disease.[2,11,20] Our results agree with those of Macklem and Mead[16] and of Morris,[2,11,20] in that neither FVC nor FEV_1 was significantly different in passive smokers and nonsmokers, but that both FEF 25 to 75 per cent and FEF 75 to 85 per cent were significantly lower in passive smokers than in nonsmokers.

In considering the relation of graded abnormality to the extent of smoke exposure, it is interesting to note that the nonsmokers in our study scored well above all other groups in the tests in Tables 1 and 3. However, there was no significant difference in the scores of the passive smokers, the smokers who did not inhale, and the light smokers. This finding suggests that if long-term small-airways dysfunction is occurring, the nonsmokers who work in a smoky environment have about the same risk of impairment as do smokers who do not inhale and smokers who inhale between one and 10 cigarettes per day. Niewoehner et al.[21] showed that further increases in exposure to cigarette smoke cause a progression from small-airways involvement to extensive bronchial and alveolar disease: the greater the exposure, the greater the involvement.

There is supporting evidence of the effects of passive smoking on small-airways function and the development of a graded abnormality according to extent of exposure to smoke. A recent study by Tager et al.[22] has shown that children living in households where parents smoked tobacco had lower mid-expiratory flow rates (FEF 25 to 75 per cent) than children who lived in households where smoking did not occur. In addition, FEF 25 to 75 per cent in children who had never smoked declined as a function of the number of parents who smoked in the household. The greater the exposure, the lower the pulmonary-function score.

Although many nonsmokers believe that exposure to tobacco smoke is irritating and generally obnoxious, our studies and Tager's show the adverse effects of passive smoking on the small-airways function of both adults and children. With these data now available, health officials and the medical profession must consider potential for small-airways dysfunction in nonsmokers chronically exposed to tobacco smoke.

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